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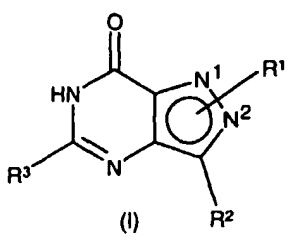
(54) Title: PDE9 INHIBITORS FOR TREATING CARDIOVASCULAR DISORDERS




(I)

(57) Abstract: The invention relates to PDE9 inhibitors for treating cardiovascular disorders. Preferred PDE9 inhibitors are compounds of formula (I) wherein $R^1$ is H or $C_{1-6}$ alkyl, wherein $R^1$ is attached to either $N^1$ or $N^2$; $R^2$ is $C_{1-6}$ alkyl optionally substituted by hydroxy or alkoxy; $C_{3-7}$ cycloalkyl optionally substituted by alkyl, hydroxy or alkoxy; a saturated 5-6-membered heterocycle optionally substituted by alkyl, hydroxy or alkoxy; $het^1$ or $Ar^1$; $R^3$ is $C_{1-6}$ alkyl optionally substituted by 1 or 2 groups independently selected from: $Ar^2$; $C_{3-7}$ cycloalkyl optionally substituted by $C_{1-6}$ alkyl; $OAr^2$; $SAr^2$; $Sar^2$; $NHC(O)C_{1-6}$ alkyl; $het^2$; xanthene; and naphthalene (I).

coronary angioplasty), peripheral vascular disease, renal disease (especially that occurring with diabetes), angina (including stable, unstable and variant (Prinzmetal) angina), myocardial ischaemia and any condition where improved blood flow leads to improved end organ function. More preferably the cardiovascular disease is systemic hypertension.

Alternatively the cardiovascular disease may be associated with other conditions, particularly hypertension associated with diabetes.

According to a further aspect there is provided the use of a PDE9 inhibitor in the manufacture of a medicament for treating a condition selected from: male sexual dysfunction (particularly male erectile dysfunction otherwise known as impotence); female sexual dysfunction (FSD) (particularly female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder, female orgasmic dysfunction, clitoral dysfunction, dysfunction caused by spinal cord injury and selective serotonin re-uptake inhibitor induced sexual dysfunction), premature labour, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, diseases and conditions of the eye (for example glaucoma and optic neuropathy, macular degeneration, elevated intra-ocular pressure, retinal or arterial occlusion), diseases characterised by disorders of gut motility (for example irritable bowel syndrome), pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, neuropathy (including autonomic and peripheral neuropathy), Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissures, haemorrhoids, hypoxic vasoconstriction and stabilisation of blood pressure during haemodialysis.

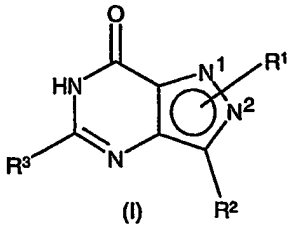
Without being bound by any theory, we believe that PDE9 inhibitors treat cardiovascular diseases by acting on the nitric oxide/cGMP pathway to mediate relaxation of vascular smooth muscle, thereby causing hypotension, augmenting vascular flow and thus protecting end organ function in disease states where blood flow is compromised.

The Caco2 flux value can be determined by standard procedures known in the art such as described in Artursson, P and Magnusson, C; J. Pharm. Sci, 79(7), 595-600, 1990.

Metabolic stability addresses the ability of the GIT or the liver to metabolise compounds during the absorption process: the first pass effect. Assay systems such as microsomes, hepatocytes etc are predictive of metabolic lability. Preferably the PDE9 inhibitors show metabolic stability in the assay system that is commensurate with an hepatic extraction of less then 0.5. Examples of assay systems and data manipulation are described in Obach, RS; Curr. Opin. Drug Disc. Devel. 4(1), 36-44, 2001 and Shibata, Y *et al.*; Drug Met. Disp. 28(12), 1518-1523, 2000.

Because of the interplay of the above processes, further support that a drug will be orally bioavailable in humans can be gained by *in vivo* experiments in animals. Absolute bioavailability is determined in these studies by administering the compound separately or in mixtures by the oral route. For absolute determinations (% absorbed) the intravenous route is also employed. Examples of the assessment of oral bioavailability in animals can be found in Ward, KW *et al.*; Drug Met. Disp. 29(1), 82-87, 2001; Berman, J *et al.*; J. Med. Chem. 40(6), 827-829, 1997 and Han KS and Lee, MG; Drug Met. Disp. 27(2), 221-226, 1999.

A preferred PDE9 inhibitor is a compound of formula I, a pharmaceutically acceptable salt, solvate or prodrug thereof

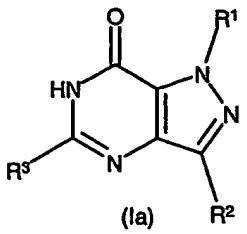


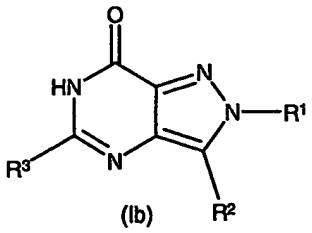

(I)

wherein

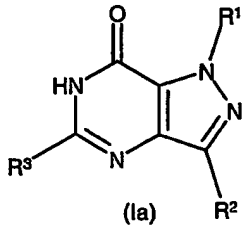
$R^1$ is H or $C_{1-6}$ alkyl, wherein $R^1$ is attached to either $N^1$ or $N^2$;

$R^2$ is $C_{1-6}$ alkyl optionally substituted by hydroxy or alkoxy; $C_{3-7}$ cycloalkyl optionally substituted by alkyl, hydroxy or alkoxy; a saturated 5-6-membered heterocycle (preferably tetrahydrofuran, tetrahydrothiophene,


(Ia)


(Ib)

A more preferred PDE9 inhibitor is a compound of formula Ia, a pharmaceutically acceptable salt, solvate or prodrug thereof


(Ia)

wherein

$R^1$ is H or $C_{1-6}$ alkyl;

$R^2$ is $C_{1-6}$ alkyl optionally substituted by hydroxy or alkoxy; $C_{3-7}$ cycloalkyl optionally substituted by alkyl, hydroxy or alkoxy; a saturated 5-6-membered heterocycle (preferably tetrahydrofuran, tetrahydrothiophene, pyrrolidine or piperidine) optionally substituted by alkyl, hydroxy or alkoxy; $het^1$ or $Ar^1$;

$R^3$ is $C_{1-6}$ alkyl optionally substituted by 1 or 2 groups independently selected from: $Ar^2$; $C_{3-7}$cycloalkyl optionally substituted by $C_{1-6}$alkyl; $OAr^2$; $SAr^2$; $NHC(O)C_{1-6}$ alkyl; $het^2$; xanthene; and naphthalene;

wherein $Ar^1$ and $Ar^2$ are independently groups of formula

wherein $R^4$, $R^5$ and $R^6$ are independently selected from: hydrogen, halo, phenoxy, phenyl, $CF_3$, $OCF_3$, $R^7$, $SR^7$ and $OR^7$, wherein $R^7$ is $C_{1-6}$ alkyl optionally substituted by $het^3$ or by a phenyl group optionally substituted by 1, 2 or 3 groups independently selected from halo, $CF_3$, $OCF_3$, $C_{1-6}$ alkyl and $C_{1-6}$alkoxy; or wherein $R^4$ and $R^5$ combine to form a 3 or 4 atom link, wherein said link may incorporate one or two heteroatoms independently selected from O, S and N; and

Unless otherwise indicated, any alkyl group may be straight or branched and is of 1 to 6 carbon atoms, preferably 1 to 4 and particularly 1 to 3 carbon atoms.

Halo means fluoro, chloro, bromo or iodo.

Preferably $R^1$ is hydrogen or $CH_3$. More preferably $R^1$ is hydrogen.

Preferably $R^2$ is $C_{3-4}$ alkyl, cyclopentyl or pyridyl. More preferably $R^2$ is 3-pyridyl.

Preferably $R^3$ is $C_{1-3}$ alkyl optionally substituted by 1 or 2 groups independently selected from: $Ar^2$, $C_{3-7}$ cycloalkyl optionally substituted by $C_{1-6}$alkyl and $het^2$. More preferably $R^3$ is $C_{1-3}$ alkyl optionally substituted by $Ar^2$. Most preferably $R^3$ is methyl substituted by $Ar^2$.

Preferably $R^4$, $R^5$ and $R^6$ are independently selected from: hydrogen, halo, phenoxy, phenyl, $CF_3$, $OCF_3$, $R^7$, $SR^7$, and $OR^7$, wherein $R^7$ is $C_{1-6}$alkyl optionally substituted by a $het^3$ group or by a phenyl group optionally substituted by 1,2 or 3 groups independently selected from halo, $CF_3$, $OCF_3$ , $C_{1-6}$ alkyl and $C_{1-6}$alkoxy; or wherein $R^4$ and $R^5$ combine to form a 3 atom link wherein said link contains an oxygen atom.

More preferably $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, halo, $CF_3$, $OCF_3$, phenoxy, and $OC_{1-6}$ alkyl optionally substituted by phenyl optionally substituted by halo, $CF_3$, $OCF_3$ or $C_{1-6}$ alkyl.

Yet more preferably $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, chloro, $OCF_3$, $CF_3$, phenoxy and $OC_{1-6}$ alkyl substituted by phenyl.

Most preferably, $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, chloro, $OCF_3$ and $OC_{1-3}$ alkyl substituted by phenyl.

Preferably $het^2$ is an aromatic 5-6 membered heterocycle containing 1 or 2 nitrogen atoms optionally containing a further heteroatom, said heterocycle being

Compounds of formula I as defined hereinabove in the various embodiments of the first aspect are novel. Therefore according to a second aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt, solvate or prodrug thereof defined hereinabove in the various embodiment of the first aspect.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups.

For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

The pharmaceutically acceptable salts of the compounds of formula I which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. Compounds of formula I which contain an acidic centre can provide pharmaceutically acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminium, calcium, magnesium and zinc salts. Alternatively organic salts can be made, for example the diethanolamine salt. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopaedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

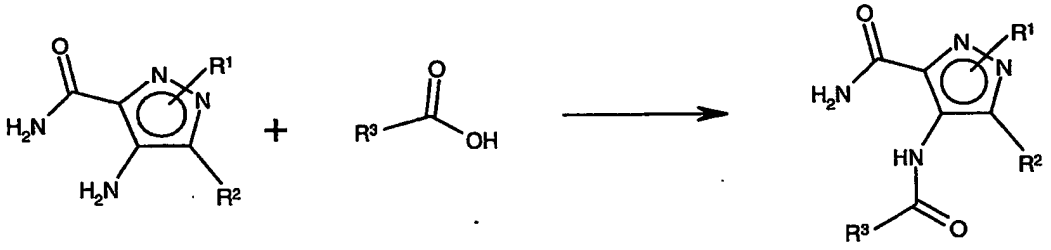
316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention. Preferred prodrugs for compounds of the invention include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$ and $^{36}Cl$, respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as $^{3}H$ or $^{14}C$ is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., $^{3}H$, and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., $^{2}H$, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

Compounds of the invention may be prepared by the following reaction schemes. In the following reaction schemes and hereafter, unless otherwise stated, $R^1$ to $R^7$

Alternatively, the reaction shown in reaction scheme 2 may be carried out by addition of a peptide coupling agent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) to a mixture of the compounds of formula III and IV. This reaction is carried out in a suitable solvent such as dichloromethane, pyridine, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or 1-methyl-2-pyrrolidinone at a temperature between 0°C and the reflux temperature of the solvent. The reaction is preferentially carried out by activation of the compound of formula IV with CDI in pyridine under refluxing conditions.

Scheme 2



(III) (IV) (II)

Compounds of general formula III may be prepared from easily obtained starting materials using processes described in the preparative examples hereinafter and described in European Patent EP0463756.

Compounds of general formula IV may be prepared from easily obtained starting materials using processes similar to those described in the preparative examples hereinafter. In addition many compounds of general formula IV are commercially available.

A pharmaceutically acceptable salt of a compound of the formula I may be readily prepared by mixing together solutions of a compound of the formula I and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

| | |
|---|---|
| Starch | 21.375 |
| Croscarmellose sodium | 3.000 |
| Magnesium Stearate | 1.500 |

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form, i.e. upon the surface or coating.

Thus tablets or capsules of the compound of the invention may contain from 0.01 mg to 500 mg (for example 10 mg to 250 mg) of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will appreciate that the compounds of the invention may be taken as a single dose as needed or desired.

The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 μg to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 μg to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

The present invention additionally comprises the combination of a PDE9 inhibitor, (particularly a compound of formula I as defined in the various embodiments of the first aspect) and one or more additional active agent selected from:

a) a PGI2 prostaglandin, such as prostacyclin or iloprost;

b) an α - adrenergic receptor antagonist compound also known as α - adrenoceptor antagonists, α-receptor antagonists or α-blockers; suitable compounds for use herein include: the α-adrenergic receptor antagonists as described in PCT application WO99/30697 published on 14th June 1998, the disclosures of which relating to α-adrenergic receptor antagonists are incorporated herein by reference and include, selective $\alpha_1$-adrenoceptor antagonists or $\alpha_2$-adrenoceptor antagonists and non-selective adrenoceptor antagonists, suitable $\alpha_1$-adrenoceptor antagonists include: phentolamine, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, dapiprazole, phenoxybenzamine, idazoxan, efaraxan, yohimbine, rauwolfa alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, terazosin, abanoquil and prazosin; $\alpha_2$-blockers from US 6,037,346 [14th March 2000] dibenamine, tolazoline, trimazosin and dibenamine; α-adrenergic receptors as described in US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063; 3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference; $\alpha_2$-adrenoceptor antagonists include: clonidine, papaverine, papaverine hydrochloride, optionally in the presence of a cariotonic agent such as pirxamine;

c) an NO-donor (NO-agonist) compound; suitable NO-donor compounds for use herein include organic nitrates, such as mono- di or tri-nitrates or organic nitrate esters including glyceryl trinitrate (also known as nitroglycerin), isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside (SNP), 3-morpholinosydnonimine molsidomine, S-nitroso- N-acetyl penicilliamine (SNAP) S-nitroso-N-glutathione (SNO-GLU), N-hydroxy - L-arginine, amylnitrate, linsidomine, linsidomine chlorohydrate, (SIN-1)

m) a PDE5 inhibitor (such as 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (sildenafil); (6*R*,12a*R*)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-*b*]indole-1,4-dione (tadalafil, IC-351); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (vardenafil); 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one; and 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one); and

n) a beta-blocker, diuretic or aldosterone antagonist.

If a combination of active agents are administered, then they may be administered simultaneously, separately or sequentially.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

In a further aspect there is provided a method of treating a cardiovascular disorder in a mammal wherein the mammal is treated with an effective amount of a PDE9 inhibitor. The preferred embodiments specified hereinabove for the first aspect extend to this aspect.

The following Examples illustrate the preparation of the compounds of formula I.

Example 1

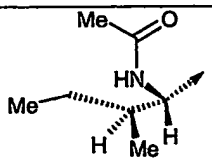
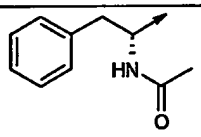
Compounds 1 to 126 of formula Ia[1] (see Table 3) were prepared, isolated and purified as follows. Each compound was characterised by a) its HPLC retention time (rt) as determined under the conditions described below, and b) by mass spectroscopy also under the conditions described below.

Table 1: Preparative HPLC Conditions:

| | | | | |
|---|---|---|---|---|
| Column | Phenomenex Luna C18, 5 µm, 150 x 10mm i.d. | | | |
| Temperature | Ambient | | | |
| Eluent A | 0.05% diethylamine (aqueous) | | | |
| Eluent B | acetonitrile | | | |
| Sample solvent | 90% dimethylsulfoxide in water | | | |
| Initial pump conditions | A% 95, B% 5, flow 6 ml/min | | | |
| Detection | Gilston 119 uv detector – 225nm | | | |
| Injection volume | 600 µl | | | |
| Gradient Timetable | Time (min) | A% | B% | Flow (ml/min) |
| | 0.0 | 95 | 5 | 6 |
| | 0.2 | 95 | 5 | 6 |
| | 7.0 | 5 | 95 | 6 |
| | 9.0 | 5 | 95 | 6 |
| | 9.1 | 95 | 5 | 6 |
| | 10.5 | 95 | 5 | 6 |

Table 2: LC-MS Conditions

| | | | | | |
|---|---|---|---|---|---|
| Column | Phenomenex Luna C18, 5 µm, 30 x 4.6mm i.d. | | | | |
| Temperature | 40°C | | | | |
| Eluent A | 0.05% diethylamine (aqueous) | | | | |
| Eluent B | acetonitrile | | | | |
| Initial pump conditions | A% 90, B% 10, flow 3ml/min | | | | |
| Injection volume | 5ml | | | | |
| Detection | products were detected by both ultraviolet and Electron Spray light Scattering (ELSD) uv: start range 210nm, End range 280nm, Range interval 5nm, threshold 0.1mAU, peakwidth 0.4min. ELSD: Sedere Dedex 55, Temperature : 40°C, Gas Flow : 2.3bar | | | | |
| Gradient Timetable | Time (min) | A% | B% | Flow (ml/min) | Pressure (bar) |
| | 0.0 | 90 | 10 | 3 | 400 |
| | 2.2 | 5 | 95 | 3 | 400 |

| Cmp | $R^3$ | rt (min) | m/z $[M+H]^+$ |
|---|---|---|---|
| 18 | isobutyl | 1.63 | 235 |
| 19 | 4-methoxybenzyl | 1.77 | 299 |
| 20 | 2,5-dimethylbenzyl | 1.93 | 297 |
| 21 | benzhydryl | 2.07 | 345 |
| 22 |  | 1.59 | 306 |
| 23 | 2-fluoro-3-trifluoromethylbenzyl | 1.95 | 355 |
| 24 | 2,4-difluorobenzyl | 1.82 | 305 |
| 25 | 2,3-difluorobenzyl | 1.86 | 305 |
| 26 | 4-fluorobenzyl | 1.80 | 287 |
| 27 | 2-[(2-imidazol-1-yl)-ethoxy]benzyl | 1.44 | 379 |
| 28 | 5-fluoro-2-trifluoromethyl-benzyl | 1.98 | 355 |
| 29 | 2,6-dichlorobenzyl | 1.97 | 338 |
| 30 | 2-chloro-6-methylbenzyl | 2.03 | 334 |
| 31 | 2-methoxybenzyl | 1.76 | 299 |
| 32 | 4-methylphenoxymethyl | 1.92 | 299 |
| 33 | 3,4-difluorobenzyl | 1.83 | 305 |
| 34 |  | 1.73 | 340 |
| 35 | 4-methylbenzyl | 1.83 | 283 |
| 36 | 2-(4-methoxyphenyl)-1-phenylethyl | 2.13 | 389 |
| 37 | napthalen-1-ylmethyl | 2.05 | 319 |
| 38 | cyclopentylmethyl | 1.77 | 261 |
| 39 | 2,6-difluorobenzyl | 1.83 | 305 |
| 40 | 3-methylbenzyl | 1.84 | 283 |
| 41 | 2,4-dimethylbenzyl | 1.99 | 297 |
| 42 | 3-fluorobenzyl | 1.82 | 287 |
| 43 | 2,3,6-trifluorobenzyl | 1.91 | 323 |
| 44 | 4-chlorophenoxymethyl | 1.97 | 320 |
| 45 | 4-phenoxybenzyl | 2.05 | 361 |

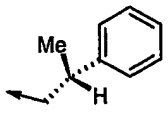
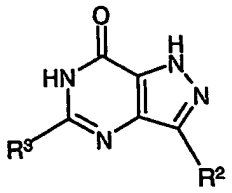
| Cmp | $R^3$ | rt (min) | m/z $[M+H]^+$ |
|---|---|---|---|
| 79 | 2-(3-methoxyphenyl)ethyl | 1.81 | 313 |
| 80 | 4-ethoxy-3-methoxybenzyl | 1.73 | 343 |
| 81 | 2-(2-methylphenyl)ethyl | 1.92 | 297 |
| 82 | 1-phenoxyethyl | 1.86 | 299 |
| 83 | 2-(3-fluorophenyl)ethyl | 1.85 | 301 |
| 84 | 2,2-diphenylethyl | 2.06 | 359 |
| 85 | 1-methylpropyl | 1.73 | 235 |
| 86 | 3,4-dimethoxybenzyl | 1.65 | 329 |
| 87 | 1-phenoxypropyl | 1.97 | 313 |
| 88 | (3-methoxyphenoxy)methyl | 1.86 | 315 |
| 89 | 2-(4-fluorophenyl)ethyl | 1.85 | 301 |
| 90 | (2-isopropyl-5-methylphenoxy)methyl | 2.19 | 341 |
| 91 | 2-(2,5-dimethoxyphenyl)ethyl | 1.77 | 343 |
| 92 | 3-(4,5-dimethoxyphenyl)propyl | 1.68 | 357 |
| 93 | 2,3-dimethoxybenzyl | 1.84 | 329 |
| 94 | (1,1-diphenyl)ethyl | 2.26 | 359 |
| 95 | 2,3,4-trimethoxybenzyl | 1.80 | 359 |
| 96 | 1-(4-chlorophenoxy)ethyl | 1.97 | 334 |
| 97 | 3,4,5-trimethoxybenzyl | 1.69 | 359 |
| 98 | (3-trifluoromethyl-phenyl)thiomethyl | 2.00 | 369 |
| 99 | 3-pyridylmethyl | 1.28 | 270 |
| 100 | (2-chloro-4-fluorophenyl)thiomethyl | 1.96 | 354 |
| 101 | 1-(4-isobutylphenyl)ethyl | 1.83 | 339 |
| 102 |   | 1.87 | 297 |
| 103 | (2-methyl-1-phenyl)propyl | 2.13 | 311 |
| 104 | 2-naphthyloxymethyl | 1.98 | 335 |
| 105 | 3-phenylpropyl | 1.87 | 297 |
| 106 | 2-(4-chlorophenyl)ethyl | 1.92 | 318 |
| 107 | 2-(4-methoxyphenyl)ethyl | 1.77 | 313 |
| 108 | (cyclopentyl)(phenyl)methyl | 2.27 | 337 |
| 109 | (2-methoxyphenoxy)methyl | 1.82 | 315 |

Table 4



(Ia²)

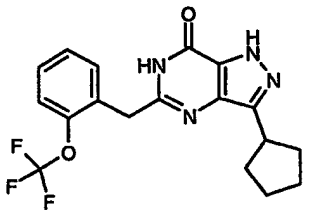
| Cmp | $R^2$ | $R^3$ | rt (min) | m/z $[M+H]^+$ |
|---|---|---|---|---|
| 127 | 3-pyridyl | 2,4-dichlorobenzyl | 1.24 | 373 |
| 128 | 3-pyridyl | cyclopropylmethyl | 0.92 | 268 |
| 129 | 3-pyridyl | 2,6-difluorobenzyl | 1.10 | 340 |
| 130 | 3-pyridyl | (4-methylcyclohexyl)methyl | 1.46 | 324 |
| 131 | 3-pyridyl | 3-chlorobenzyl | 1.23 | 339 |
| 132 | 3-pyridyl | 2-ethoxybenzyl | 1.24 | 348 |
| 133 | 3-pyridyl | 2-phenoxybenzyl | 1.46 | 396 |
| 134 | 3-pyridyl | 2,3,5-trifluorobenzyl | 1.18 | 358 |
| 135 | 3-pyridyl | 3-fluoro-4-trifluoromethylbenzyl | 1.37 | 390 |
| 136 | 3-pyridyl | 5-fluoro-2-trifluoromethylbenzyl | 1.29 | 390 |
| 137 | 3-pyridyl | 5-bromo-2-methoxybenzyl | 1.30 | 413 |
| 138 | 3-pyridyl | 2-benzyloxybenzyl | 1.42 | 410 |
| 139 | butyl | 2-methylbenzyl | 1.44 | 297 |
| 140 | butyl | 2-methoxybenzyl | 1.36 | 313 |
| 141 | butyl | 2-chlorobenzyl | 1.45 | 318 |
| 142 | butyl | 2-fluorobenzyl | 1.34 | 301 |
| 143 | butyl | 2-chloro-6-fluorobenzyl | 1.47 | 336 |
| 144 | butyl | 2,6-dichlorobenzyl | 1.56 | 352 |
| 145 | butyl | 4-butoxybenzyl | 1.72 | 355 |
| 146 | butyl | cyclopropylmethyl | 1.14 | 247 |
| 147 | butyl | 2,6-difluorobenzyl | 1.38 | 319 |
| 148 | butyl | 2-ethoxybenzyl | 1.48 | 327 |
| 149 | butyl | 3-benzyloxybenzyl | 1.67 | 389 |
| 150 | isopropyl | 2,4,5-trifluorobenzyl | 1.36 | 323 |
| 151 | isopropyl | 2,4-dichlorobenzyl | 1.54 | 338 |

| Cmp | $R^2$ | $R^3$ | rt (min) | m/z $[M+H]^+$ |
|---|---|---|---|---|
| 185 | cyclopentyl | 2-methylbenzyl | 1.52 | 309 |
| 186 | cyclopentyl | isobutyl | 1.33 | 261 |
| 187 | cyclopentyl | 2-methoxybenzyl | 1.44 | 325 |
| 188 | cyclopentyl | 2-chlorobenzyl | 1.52 | 330 |
| 189 | cyclopentyl | 2-fluorobenzyl | 1.42 | 313 |
| 190 | cyclopentyl | 2-chloro-6-fluorobenzyl | 1.53 | 347 |
| 191 | cyclopentyl | 2-methylbutyl | 1.49 | 275 |
| 192 | cyclopentyl | 2-trifluoromethylbenzyl | 1.62 | 363 |
| 193 | cyclopentyl | 2,4-dichlorobenzyl | 1.70 | 364 |
| 194 | cyclopentyl | 2,6-dichlorobenzyl | 1.61 | 364 |
| 195 | cyclopentyl | 4-butoxybenzyl | 1.80 | 367 |
| 196 | cyclopentyl | 5-cyclopropylmethyl | 1.22 | 259 |
| 197 | cyclopentyl | 2,6-difluorobenzyl | 1.44 | 331 |
| 198 | cyclopentyl | 2,4,6-trimethoxybenzyl | 1.47 | 385 |
| 199 | cyclopentyl | 3-chlorobenzyl | 1.55 | 330 |
| 200 | cyclopentyl | 2,5-dimethoxybenzyl | 1.41 | 355 |
| 201 | cyclopentyl | 2-ethoxybenzyl | 1.55 | 339 |
| 202 | cyclopentyl | 2-phenoxybenzyl | 1.75 | 387 |
| 203 | cyclopentyl | 3-fluoro-4-trifluoromethylbenzyl | 1.67 | 381 |
| 204 | cyclopentyl | 2-benzyloxybenzyl | 1.73 | 401 |
| 205 | cyclopentyl | 2-(2-imidazol-1-yl-ethoxy)benzyl | 1.20 | 405 |
| 206 | cyclopentyl | 3-benzyloxybenzyl | 1.73 | 401 |
| 207 | cyclopentyl | n-propyl | 1.19 | 247 |
| 208 | cyclopentyl | 2,3-dihydro-benzofuran-5-ylmethyl | 1.35 | 337 |
| 209 | isopropyl | 2-chlorobenzyl | 1.25 | 304 |
| 210 | isopropyl | 2-chloro-6-fluoro-benzyl | 1.25 | 322 |
| 211 | isopropyl | 2,6-dichlorobenzyl | 1.33 | 338 |
| 212 | isopropyl | 2,5-dimethoxybenzyl | 1.15 | 329 |
| 213 | 3-pyridyl | 2-trifluoromethylbenzyl | 1.26 | 372 |
| 214 | 3-pyridyl | 2,6-dichlorobenzyl | 1.24 | 373 |
| 215 | 3-pyridyl | 2,5-dimethoxybenzyl | 1.13 | 364 |
| 216 | 3-pyridyl | n-propyl | 0.89 | 256 |
| 217 | 3-pyridyl | 2,3-dihydrobenzofuran-5-ylmethyl | 1.07 | 346 |

| Cmp | $R^2$ | $R^3$ | rt (min) | m/z $[M+H]^+$ |
|---|---|---|---|---|
| 251 | isobutyl | 2,5-dimethoxybenzyl | 1.31 | 343 |
| 252 | isobutyl | propyl | 1.06 | 235 |
| 253 | isobutyl | 2,4,6-trimethylbenzyl | 1.64 | 325 |
| 254 | isobutyl | 2,4,6-trimethoxybenzyl | 1.38 | 373 |
| 255 | cyclopentyl | 2,4,6-trimethylbenzyl | 1.74 | 337 |

Example 3

3-Cyclopentyl-5-(2-trifluoromethoxybenzyl)-1,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one (Compound 256)

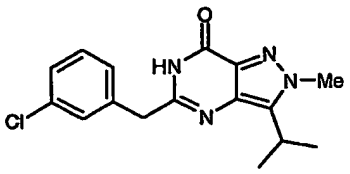


The product from preparation 28 (120mg, 0.303mmol) and potassium tert-butoxide (102mg, 0.909mmol) were suspended in isopropyl alcohol (5ml) and the reaction was heated to reflux under nitrogen for 18h. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (20ml) and water (20ml). The aqueous phase was removed, acidified to pH2 with 2N HCl, and extracted with ethyl acetate (2x15ml). The combined organic extracts were washed with saturated sodium carbonate solution (3x10ml), dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with dichloromethane : methanol (95 : 5, by volume) to give the title product (21mg) as an off-white solid, $^1H$ NMR (400MHz, DMSO-d6): $\delta$ = 7.36-7.41 (2H, m), 7.29-7.36 (2H, m), 3.97-4.03 (2H, brs), 2.39-2.45 (1H, m, partially masked by solvent), 1.82-1.94 (2H, m), 1.66-1.79 (2H, m), 1.58-1.65 (2H, m), 1.49-1.58 (2H, m) ppm; LRMS (electrospray) : m/z $[M-H]^+$ 377.

Compounds 257 to 261 of formula $Ia^2$ were prepared by methods analogous to Example 3 from the starting materials indicated in Table 5 below.

Example 4

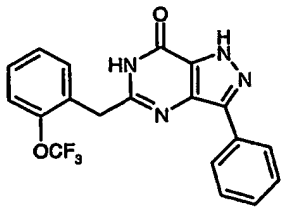
5-(3-Chlorobenzyl)-3-isopropyl-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one (Compound 262)



To a mixture of the product from Preparation 31 (0.2g) in isopropyl alcohol (6 ml) was added potassium tert-butoxide (2.2 g) and stirred at 85°C for 24 hours and then at room temperature for 3 days. The resulting heterogeneous mixture was concentrated *in vacuo*. Water (10 ml) was added to the residue followed by 3 drops of concentrated hydrochloric acid. The resulting precipitate was taken up in ethyl acetate (150 ml) and washed with water (x2). The organic extract was dried ($MgSO_4$) and concentrated to give a solid which was purified by column chromatography using silica gel eluting with a solvent gradient of dichloromethane : methanol (100:0 changing to 99:1 changing to 98:2) to give the title product ; $^1H$ NMR (400MHz,-$CD_3OD$): $\delta$ = 7.39 (1H, s), 7.28 (1H, s), 7.12 (2H, m), 4.01 (3H, s), 3.96 (2H, s), 3.26 (1H, m), 1.45 (6H, d).

Example 5

5-(2-Trifluoromethoxybenzyl)-3-phenyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one (compound 263)

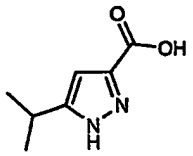


Palladium tetrakis triphenylphosphine (22mg, 5 mole %) was added to a nitrogen-purged solution of the product from preparation 36 (164 mg, 0.376 mmol), phenyl boronic acid (69 mg, 0.56 mmol), sodium carbonate (119 mg, 1.13 mmol as a solution in 0.8 ml water) in ethylene glycol dimethyl ether (3 ml). The mixture was heated at 83°C for 18 h. On cooling, the mixture was diluted with ethyl acetate/tetrahydrofuran and washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC

was removed. The organic phase was washed with water (2x200ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a solvent gradient of pentane : ethyl acetate (4 : 1 changing to 2 : 1, by volume) to give the title product (18.9g) as a white solid; $^1H$ NMR (400MHz, $CDCl_3$): $\delta$ = 10.80-10.95 (1H, brs), 6.61 (1H, s), 4.33-4.40 (2H, quart), 2.98-3.08 (1H, quin), 1.35-1.41 (3H, t), 1.24-1.32 (6H, d) ppm; LRMS (electrospray) : m/z $[M-H]^+$ 181.

Preparation 3

5-Isopropyl-1H-pyrazol-3-carboxylic acid

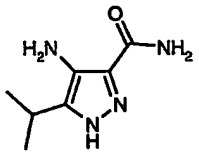


The product from preparation 2 (18.9g, 104mmol) and 1M NaOH solution (260ml, 259mmol) were dissolved in 1,4-dioxan (300ml), the reaction was heated to 50°C under nitrogen and stirred for 3h. The reaction mixture was cooled, adjusted to pH 2 using concentrated hydrochloric acid and the solvent was removed under reduced pressure. The residual solid was azeotroped with toluene (2x30ml), dissolved in ethyl acetate (500ml) and washed with water (200ml). The aqueous phase was removed, extracted with ethyl acetate (2x200ml) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was azeotroped with dichloromethane (2x50ml) to give the title product (14.7g) as a white solid; $^1H$ NMR (400MHz, DMSO-D6): $\delta$ = 12.50-13.30 (2H, brs), 6.42 (1H, s), 2.84-2.94 (1H, quin), 1.15-1.19 (6H, d) ppm; LRMS (electrospray): m/z $[M-H]^+$ 153.

(300ml), concentrated to approximately 80ml under reduced pressure and the precipitate was isolated by filtration. The filtrate was washed with water and dried *in vacuo* to give the title product (3.1g) as an orange solid; $^1$H NMR (400MHz, DMSO-D6): δ = 7.94-7.99 (1H, brs), 7.68-7.72 (1H, brs), 3.45-3.55 (1H, m), 1.24-1.30 (6H, d) ppm; LRMS (electrospray) : m/z $[M+Na]^+$ 221, $[M-H]^+$ 197.

Preparation 6

4-Amino-5-isopropyl-1H-pyrazol-3-carboxylic acid amide

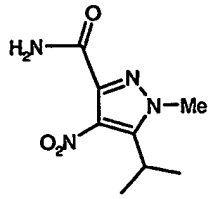


The product from preparation 5 (3g, 15.1mmol) and 10% palladium on carbon (500mg) in ethanol (30ml) were stirred under hydrogen (50psi) at room temperature for 18h. The reaction mixture was filtered and the solid was washed with methanol (50ml), dichloromethane (50ml), ethanol (50ml) and ethyl acetate (50ml). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with dichloromethane : methanol (9 : 1, by volume) to give the title product (2.6g) as an off-white solid; $^1$H NMR (400MHz, DMSO-D6): δ = 12.20-12.30 (1H, brs), 7.02-7.14 (1H, brs), 6.85-6.95 (1H, brs), 4.30-4.46 (2H, brs), 2.90-3.00 (1H, m), 1.15-1.21 (6H, d) ppm; LRMS (electrospray) : m/z $[M-H]^+$ 167, $[2M-H]^+$ 335; Anal. Found C, 49.86; H, 7.21; N, 33.07. $C_7H_{12}N_4O$ requires C, 49.99; H, 7.19; N, 33.31%.

Preparations 7 to 10 of general formula IIIa were prepared by methods analogous to Preparations 1 to 6 from the starting materials indicated in Table 6.

Preparation 12

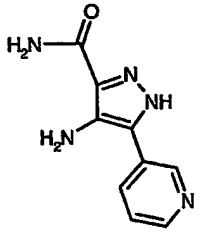
5-Isopropyl-1-methyl-4-nitro-1H-pyrazole-3-carboxamide



To a mixture of the product from preparation 5 (150 mg) in acetonitrile (6 ml) was added ceasium carbonate (107 mg) followed by iodomethane (40 µl). The mixture was heated at 77 °C overnight. The mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate (200 ml) and washed with brine. The organic extracts were dried ($MgSO_4$), the solvent was removed and the residue purified by chromatography using silica gel eluting with pentane : ethyl acetate (100:0 to 15:1 to 1:1); $^1H$ NMR (400MHz, $CDCl_3$): $\delta$ = 6.50 (1H, br.s), 5.65 (1H, br.s), 3.89 (3H, s), 3.43 (1H, m), 1.36 (6H, d).

Preparation 13

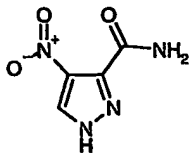
4-Amino-5-(3-pyridyl)-1H-pyrazole-3-carboxamide



A solution of the product from preparation 14 (1 g) in 0.88M ammonia (100 ml) were heated at 100°C in a bomb overnight. The mixture was concentrated *in vacuo* and the residue was purified by chromatography using silica gel eluting with dichloromethane : methanol (9:1) to give the title product (709 mg).

Preparation 16

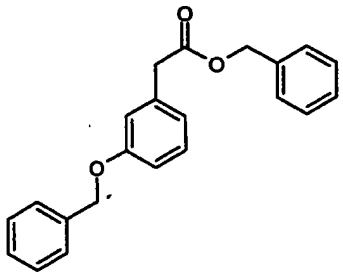
4-Nitro-1H-pyrazol-3-carboxylic acid amide



The title product was prepared by an analogous method to Preparation 5 starting from 4-nitro-1H-pyrazol-3-carboxylic acid (Sigma-Aldrich Chemical Co.)

Preparation 17

(3-Benzyloxy-phenyl)-acetic acid benzyl ester

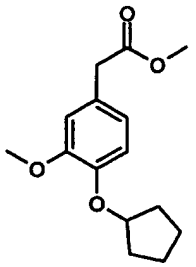


3-Hydroxy-phenyl-acetic acid (15.3g, 101mmol), benzyl bromide (36.2g, 202mmol) and potassium carbonate (29.2g, 202mmol) were suspended in dimethylformamide (300ml) and the reaction was heated to reflux under nitrogen for 44h. The reaction mixture was cooled, filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (200ml) and water (200ml), and the aqueous phase was extracted with ethyl acetate (2x200ml). The combined organic extracts were washed with brine (200ml), dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with pentane : ethyl acetate (95 : 5, by volume) to give the title product (10.7g) as a white solid.

(100ml), dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a solvent gradient of cyclohexane : ethyl acetate (80 : 20 changing to 70 : 30, 60 : 40 and finally 1 : 1, by volume) to give the title product (23g) as a yellow oil; $^1H$ NMR (400MHz, $CDCl_3$): $\delta$ = 6.82-6.85 (1H, d), 6.80 (1H, s), 6.76-6.79 (1H, d), 5.49 (1H, s), 3.86 (3H, s), 3.66 (3H, s), 3.53 (2H, s) ppm; LRMS (electrospray) : m/z $[M+Na]^+$ 219.

Preparation 20

(4-Cyclopentyloxy-3-methoxy-phenyl)-acetic acid methyl ester



Cyclopentanol (7.7ml, 85mmol) and triphenylphosphine (28g, 107mmol) were added to a solution of the product from preparation 19 (14g, 71mmol) in tetrahydrofuran (280ml) under nitrogen at 0°C. Diethylazodicarboxylate (15.7ml, 100mmol) was then added dropwise and the reaction was allowed to warm to room temperature and stirred for 44h. The solvent was removed under reduced pressure, pentane (200ml) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with a solvent gradient of cyclohexane : ethyl acetate (90 : 10 changing to 85 : 15, by volume) to give the title product (12.4g) as a colourless oil; $^1H$ NMR (400MHz, $CD_3OD$): $\delta$ = 6.79-6.85 (2H, m), 6.73-6.79 (1H, d), 4.73-4.79 (1H, brs), 3.79 (3H, s), 3.64 (3H, s), 3.53 (2H, s), 1.74-1.89 (6H, m), 1.56-1.67 (2H, m) ppm; LRMS (electrospray) : m/z $[M+Na]^+$ 287; Anal. Found C, 68.01; H, 7.74. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%.

product (52.6g) as a white solid; $^1$H NMR (250MHz, $CD_3OD/D_2O$): $\delta$ = 6.88-7.03 (3H, m), 3.48-3.68 (2H, s), 2.23 (6H, s) ppm.

Preparation 23

Benzene sulfonic acid 2-chloro-ethyl ester

2-Chloroethanol (1168g, 14.5 mol) and benzene sulfonyl chloride (2780g, 15.7 mol) were stirred together at -5°C and pyridine (2158g, 27.2mol) was added over a 3h period, maintaining the temperature below 0°C. The reaction was stirred for a further 3h at –5-0°C and was then allowed to warm to room temperature over 18h. After pouring into a mixture of ice (10l) and water (10l) the reaction was stirred for 15min, extracted with ether (10l) and the organic phase was washed with 5N HCl (2x2l) and water (2x4l). It was then dried over $MgSO_4$ and concentrated under reduced pressure to give the title product (1921g) as an orange oil; $^1$H NMR (250MHz, $CDCl_3$): $\delta$ = 7.78-8.02 (2H, m), 7.58-7.78 (3H, m), 4.20-4.45 (2H, t), 3.60-3.81 (2H, t) ppm.

Preparation 24

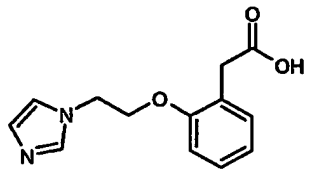
2-Hydroxy-phenyl-acetic acid ethyl ester

2-Hydroxy-phenyl-acetic acid (30.4g, 0.2mol) was dissolved in chloroform (200ml) and thionyl chloride (50ml, 0.2mol) was added. The reaction was gently refluxed for 2h, upon which the mixture was concentrated under reduced pressure. The residue was slowly poured into ethanol (200ml) maintaining a temperature of 10-20°C. The solvent was removed under reduced pressure and the residue was purified by thermal distillation to give the title product (31.6g) as a yellow oil, b.p. 146-150°C; $\nu_{max}$ (thin film) 1710cm$^{-1}$ (C=O, ester).

crude product was converted to the hydrochloride salt and purified by recrystalisation from isopropyl alcohol/ethyl acetate to give the title product as its hydrochloride salt, m.p. 129.5-130.5 °C.

Preparation 27

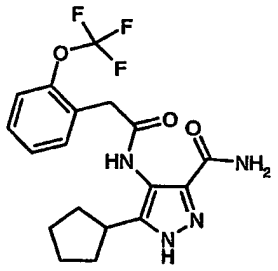
[2-(2-Imidazol-1-yl-ethoxy)-phenyl]-acetic acid



The product from Preparation 26 (3.5g, 113mmol) was stirred in 50% aqueous hydrochloric acid (20ml) at 100°C for 6h. After cooling to room temperature the solvent was removed under reduced pressure and the residue was recrystallised from isopropyl alcohol to give the title product (2.73g) as a white solid; m.p. 146-147°C; $\nu_{max}$ (thin film) 3410 (O-H), 1722cm$^{-1}$ (C=O, acid); Anal. Found C, 54.89; H, 5,25; N, 9.80. $C_{13}H_{14}N_2O_3$. 1mol HCl requires C, 55.22; H, 5.35; N, 9.91%.

Preparation 28

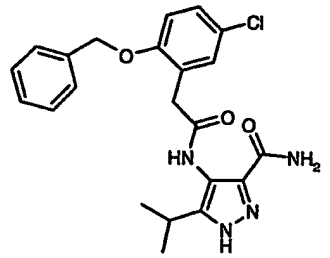
5-Cyclopentyl-4-[2-(2-trifluoromethoxy-phenyl)-acetylamino]-1H-pyrazole-3-carboxylic acid amide



Carbonyldiimidazole (84mg, 0.515mmol) was added to a solution of 2-trifluoromethyoxyphenyl acetic acid (113mg, 0.515mmol) in tetrahydrofuran (4ml) under nitrogen at room temperature, and the mixture was stirred for 3h. The product from preparation 10 (100mg, 0.515mmol) was then added and the reaction was stirred for 18h. The reaction mixture was diluted with water (20ml), acidified to pH2 with 2N HCl and extracted with ethyl acetate (2x20ml). The combined organic extracts were dried over $MgSO_4$ and concentrated under

Preparation 35

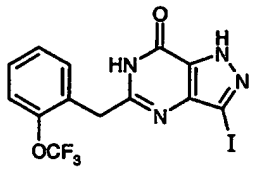
4-{[(2-Benzyloxy-5-chloro-phenyl)acetyl]amino}-5-isopropyl-1H-pyrazole-3-carboxamide



1-Propylphosphonic acid cyclic anhydride (0.39 ml of a 50 % solution in ethyl acetate, 0.57mmol) was added to a solution of 2-benzyloxy-5-chlorophenyl acetic acid (132mg, 0.475mmol), the product from preparation 6 (80mg, 0.475mmol) and triethyl amine (0.132 ml, 0.95 mmol) in dimethylformamide (4ml) under nitrogen at room temperature and the reaction was stirred for 18h. The reaction mixture was diluted with brine (20 ml) and extracted with ethyl acetate (2x20ml). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the title product (191mg) as an off-white solid; LCMS: m/z 427 $[M+H]^+$.

Preparation 36

5-(2-Trifluoromethoxybenzyl)-3-iodo-1,6-dihydro-pyrazolo[4,3-*d*]pyrimidin-7-one



N-Iodosuccinimide (326 mg, 1.45 mmol) was added to a solution of the product from preparation 37 (300 mg, 0.967 mmol) in dry dimethylformamide (5 ml) at room temperature. The mixture was heated at 55°C for 18 h, cooled and concentrated *in vacuo*. The residue was dissolved in ethyl acetate/tetrahydrofuran and washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (1→2% MeOH/$CH_2Cl_2$) to afford the title product (169 mg) as an off-white solid;

Preparation of Assay Buffers and Solutions

- Buffer A was prepared containing Tris.HCl (20 mM), $MgCl_2.6H_2O$ (5 mM) in water. The resulting solution was used at 30°C and had a pH of pH=7.4.
- Buffer B was prepared containing Bovine Serum Albumin (2 mg/ml) (BSA) in Buffer A. It was prepared fresh and filter sterilised.
- PDE9 enzyme solution was prepared in Buffer B (dilution factor determined such that no more than 30% breakdown of substrate occurred, but typically 1:35,000).
- cGMP substrate was prepared from a 50nM stock of guanosine 3':5'-cyclic monophosphate (cGMP) prepared to give final assay concentration of 25nM (to prepare 5ml based on specific activity of labelled substrate of 16.0Ci/mmol; 1mCi/ml, add 4µl [$^3$H]cGMP to 4.996ml Buffer A).
- SPA beads were prepared by creating a suspension of beads in water (20 mg/ml) (28ml per pack) containing 3mM cold cGMP to effectively quench the reaction.

Preparation of Compounds

The compounds of the invention were diluted by a factor of 50 (i.e. 2µl in 100µl) when constituted in the final assay mix. Compound stock was prepared at 4mM in DMSO. Dilute 1/8 with DMSO to give 500µM solutions.

A 4mM stock of standard inhibitor was prepared in DMSO. The standard inhibitor chosen was 5-(3-bromobenzyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. The solution was further diluted with DMSO to give a 500µM solution.

For 10-point ½ log dilution, 200µl of compound and standard solutions were dispensed into a 96-well V-bottom plate and the compounds further diluted with DMSO in steps of 1:3.16. Following serial dilution, 2µl of compound dilutions were dispensed in duplicate into microtitre plates with 2µl DMSO added to controls as shown below.

ventricle homogenate by chromatographic separation of a high speed centrifugation supernatant fraction; ii) the cGMP substrate (1μM) was prepared by combining 0.436 ml of a 10 μM stock of unlabelled guanosine 3':5'-cyclic monophosphate (cGMP) with 10 μM [3H]cGMP (15.6Ci/mmol) and 4.554 ml Buffer A; the final assay concentration of cGMP in the assay being 0.5 μM, iii) the PDE1 inhibitor used as a standard was 5-[4-(N,N-diethylamino)benzyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, and iv) during the procedure the plates were incubated for 30 minutes.

The compounds of the invention were tested using the above assays and found to inhibit the PDE9 enzyme.

Compounds 1-21, 23-31, 33-77, 118, 127-208, 213, 214, 224 and 256-263 were found to have a greater than 40% inhibition against PDE9 at a concentration of 1μM .

In particular, compound 52 was found to have an IC50 against PDE9 of 126 nM; compound 204 was found to have an IC50 against PDE9 of 143 nM; and compound 258 was found to have an IC50 against PDE9 of 141 nM. Compounds 52, 204 and 258 were all greater than 10 fold selective for PDE9 over PDE1.

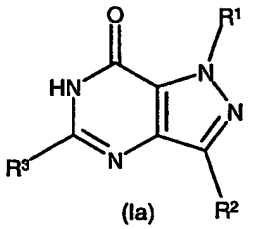
optionally substituted by 1, 2 or 3 groups independently selected from halo and $C_{1-6}$ alkyl;

with the provisos that when

a) $R^1$ is attached to $N^1$, $R^1$ is $C_{1-3}$ alkyl and $R^2$ is propyl then $R^3$ is not methyl substituted by $Ar^1$, and

b) $R^1$ is attached to $N^1$, $R^1$ is $C_{1-6}$ alkyl and $R^2$ is methyl then $R^3$ is not $C_{1-4}$alkyl substituted by $Ar^1$.

2 A compound according to claim 1 wherein the compound is of formula Ia, a pharmaceutically acceptable salt, solvate or prodrug thereof



(Ia)

wherein

$R^1$ is H or $C_{1-6}$ alkyl;

$R^2$ is $C_{1-6}$ alkyl optionally substituted by hydroxy or alkoxy; $C_{3-7}$ cycloalkyl optionally substituted by alkyl, hydroxy or alkoxy; a saturated 5-6-membered heterocycle optionally substituted by alkyl, hydroxy or alkoxy; $het^1$ or $Ar^1$;

$R^3$ is $C_{1-6}$ alkyl optionally substituted by 1 or 2 groups independently selected from: $Ar^2$; $C_{3-7}$cycloalkyl optionally substituted by $C_{1-6}$alkyl; $OAr^2$; $SAr^2$; $NHC(O)C_{1-6}$ alkyl; $het^2$; xanthene; and naphthalene;

wherein $Ar^1$ and $Ar^2$ are independently groups of formula


wherein $R^4$, $R^5$ and $R^6$ are independently selected from: hydrogen, halo, phenoxy, phenyl, $CF_3$, $OCF_3$, $R^7$, $SR^7$ and $OR^7$, wherein $R^7$ is $C_{1-6}$ alkyl optionally substituted by $het^3$ or by a phenyl group optionally substituted by 1, 2 or 3 groups independently selected from halo, $CF_3$, $OCF_3$, $C_{1-6}$ alkyl and $C_{1-6}$alkoxy; or wherein $R^4$ and $R^5$ combine

9 A compound according to any preceding claim wherein $R^3$ is methyl substituted by $Ar^2$.

10 A compound according to any preceding claim wherein $R^4$, $R^5$ and $R^6$ are independently selected from: hydrogen, halo, phenoxy, phenyl, $CF_3$, $OCF_3$, $R^7$, $SR^7$, and $OR^7$, wherein $R^7$ is $C_{1-6}$alkyl optionally substituted by a $het^3$ group or by a phenyl group optionally substituted by 1, 2 or 3 groups independently selected from halo, $CF_3$, $OCF_3$, $C_{1-6}$ alkyl and $C_{1-6}$alkoxy; or wherein $R^4$ and $R^5$ combine to form a 3 atom link wherein said link contains an oxygen atom.

11 A compound according to any preceding claim wherein $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, halo, $CF_3$, $OCF_3$, phenoxy, and $OC_{1-6}$ alkyl optionally substituted by phenyl optionally substituted by halo, $CF_3$, $OCF_3$ or $C_{1-6}$ alkyl.

12 A compound according to any preceding claim wherein $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, chloro, $OCF_3$, $CF_3$, phenoxy and $OC_{1-6}$ alkyl substituted by phenyl.

13 A compound according to any preceding claim wherein $R^4$, $R^5$ and $R^6$ are independently selected from hydrogen, chloro, $OCF_3$ and $OC_{1-3}$ alkyl substituted by phenyl.

14 A compound according to any one of claims 1 to 7 wherein $het^2$ is an aromatic 5-6 membered heterocycle containing 1 or 2 nitrogen atoms optionally containing a further heteroatom, said heterocycle being optionally substituted by 1, 2 or 3 substituents, each independently selected from $C_{1-6}$ alkyl, halo and phenyl optionally substituted by 1, 2 or 3 groups independently selected from halo and $C_{1-6}$ alkyl.

15 A compound according to claim 14 wherein $het^2$ is an aromatic 5-membered heterocycle containing 1 or 2 nitrogen atoms (optionally

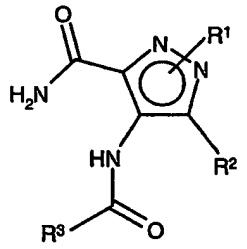
a medicament for treating or preventing a cardiovascular disorder, disease or condition.

20 The use according to claim 19, a pharmaceutically acceptable salt or solvate thereof, wherein the disorder, disease or condition is systemic hypertension.

21 A compound defined in any one of claims 1 to 18, a pharmaceutically acceptable salt or solvate thereof, for use as a medicament.

22 A pharmaceutical composition comprising a compound defined in any one of claims 1 to 18, a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier.

23 A process for preparing a compound of formula I as defined in any one of claims 1 to 18 comprising reacting a compound of formula II with a suitable reagent to effect cyclisation.




(II)

24 The use of a PDE9 inhibitor in the manufacture of a medicament for treating or preventing a cardiovascular disorder, disease or condition.

25 The use according to claim 24 wherein the PDE9 inhibitor has a greater than 40% inhibition against PDE9 at a concentration of 1 micromolar.

26 The use according to claim 25 wherein the PDE9 has a selectivity for PDE9 over PDE1 of greater than 10.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 3 939 161 A (RATAJCZYK JAMES DANIEL ET AL) 17 February 1976 (1976-02-17) claim 1; example 16 | 1-26 |
| X | HAMILTON H W ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF PYRAZOLOU4,3-D PYRIMIDIN-7-ONES AS ADENOSINE RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 30, no. 1, 1987, pages 91-96, XP002040681 ISSN: 0022-2623 example 5B | 1 |
| X | DEWALD, H.A. ET AL: "Synthesis and Potential Antipsychotic Activity of 1H-Imidazo'1,2-c!pyrazolo'3,4-e! pyrimidines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, 1988, pages 454-461, XP002224492 example 2G | 1 |
| A | WO 00 12504 A (NIEWOEHNER ULRICH ;HANING HELMUT (DE); BAYER AG (DE); BISCHOFF ERW) 9 March 2000 (2000-03-09) page 20 -page 23; claim 1 | 1-26 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 24-26

Present claims 24-26 relate to uses of compounds defined by reference to a desirable property, namely inhibition of PDE9.

These claims cover the use of all compounds revealing inhibition of PDE9 as characteristic feature, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of claims 24-26 which relate to compounds according to formula (I).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 02/04385

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0012504 A | 09-03-2000 | DE 19838705 A1 | 02-03-2000 |
| | | AU 5516399 A | 21-03-2000 |
| | | CA 2342109 A1 | 09-03-2000 |
| | | WO 0012504 A2 | 09-03-2000 |
| | | EP 1107968 A2 | 20-06-2001 |
| | | JP 2002523507 T | 30-07-2002 |
| | | US 6458796 B1 | 01-10-2002 |